Journal of Cardiology 68 (2016) 1–6

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Review

Overview of complications during pharmacological spasm provocation tests

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ARTICLE INFO

Article history:
Received 6 January 2016
Received in revised form 1 March 2016
Accepted 4 March 2016
Available online 24 May 2016

Keywords:
Acetylcholine
Ergonovine
Spasm
Complication

ABSTRACT

Pharmacological spasm provocation tests are invasive methods and we always have the potential to encounter complications when performing these tests. In 1980, Buxton et al. reported three deaths when they performed intravenous ergonovine testing. However, we now employ the intracoronary ergonovine test instead of the intravenous injection of ergonovine from a safety procedure point of view. Past serious major complications of intravenous ergonovine tests, intracoronary ergonovine tests, and intracoronary acetylcholine tests were 0.31% (26/8419), 0.51% (11/2173), and 0.95% (148/15,527), respectively. Selective intracoronary testing had the serious major complications in 0.89% of patients including just one death (0.006%) and two acute myocardial infarctions (0.01%). Selective spasm provocation tests had no additional risks compared with performing diagnostic coronary angiography alone. In the Western countries, the pharmacological spasm provocation tests are not familiar in the clinic except for some specialized institutions. We need international clinical studies using the same protocol of spasm provocation tests to compare the frequency, clinical features, and prognosis of acetylcholine- or ergonovine-provoked coronary spasm between Western and Asian countries. And we hope that Western guidelines give spasm provocation testing a class I indication similar to Japanese Circulation Society guidelines because coronary artery spasm may have fewer racial differences and borders.

Contents

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http://dx.doi.org/10.1016/j.jjcc.2016.03.005
0914-5087/

Introduction

Coronary artery spasm may be involved in the pathogenesis of various cardiac disorders, such as acute coronary syndrome, unstable angina, serious fatal arrhythmia, sudden cardiac death, syncope, transient heart failure, atypical chest pain and so on [1–7]. In these clinical situations, we decided to perform spasm provocation tests of acetylcholine (ACh) or ergonovine (ER) in patients suspected of vasospastic angina as invasive methods. ACh acts through muscarinic receptors and ER acts by way of serotogenic receptors. Different mediators may have potential to cause different coronary responses. Pharmacological spasm provocation tests may have some complications because these tests are invasive examinations. Buxton et al. reported three deaths when they performed the intravenous ER testing in 1980 [8]. Hackett et al. and Ishise et al. reported the usefulness of intracoronary injection of ER in diagnosing patients with vasospastic angina in 1987 [9,10]. Yasue and Okumura reported the usefulness of intracoronary administration of ACh in patients with variant angina in 1988 [11–13]. Instead of intravenous injection of ER, cardiologists have selected the employment of intracoronary administration methods of ACh and ER. However, there are some controversies concerning the complications of pharmacological spasm provocation tests. In the clinic, cardiologists in Asian countries are now interested in performing spasm provocation testing [14,15], but cardiologists in Western countries are not familiar with performing pharmacological spasm provocation tests except in some specialized hospitals. According to the Japanese Circulation Society (JCS) guidelines for vasospastic angina established in 2008, selective methods of ACh and ER tests are recommended to diagnose patients when suspecting coronary spasm as invasive methods [16]. In the JCS guidelines, the pharmacological spasm provocation test is defined as class I, whereas the European Society of Cardiology (ESC) guideline and the American College of Cardiology (ACC)/American Heart Association (AHA) guideline give the spasm provocation testing class IIa and class IIb, respectively [17,18]. In this review, we summarize the complications of ACh and ER tests in the past. Moreover, we also reevaluate the spasm provocation tests with regard to the clinical grading in the guidelines.

In our experience

From January 1991 to June 2015, we performed 1664 intracoronary ACh spasm provocation tests and 1164 intracoronary ER spasm provocation tests. During this period, we performed a total 7746 coronary angiography procedures including 2053 percutaneous coronary intervention procedures and 5693 diagnostic/follow-up cardiac catheterizations. We performed ACh spasm provocation tests in more than a quarter of patients with diagnostic/follow-up catheterization (29.2%; 1664/5693) and ER tests in approximately one fifth of those patients (20.4%; 1164/5693). We tried to perform the selective spasm provocation tests to examine the incidence of provoked spasm in patients who had undergone coronary angiography as much as possible. And we also tried to investigate the difference of coronary response between ACh and ER as a spasm provocation agent. During the same period, we also performed both ACh and ER tests in 508 patients and adding intracoronary injection of ACh just after ER tests in 282 patients. ER (ergometrine injection F, 0.2 mg/mL; Fuji Seiyaku, Tokyo, Japan) in 0.9% warm saline solution was injected in 10 μg/min for 4 min for a maximal dose of 40 μg into the right coronary artery and 16 μg/min over 4 min for a total dose of 64 μg into the left coronary artery, with at least a 5-min interval between each injection. ACh (Neucholin-A, 30 mg/2 mL; ZERIA Pharmaceutical Co. Ltd, Tokyo, Japan) was injected in incremental doses of 20, 50, and 80 μg into the right coronary artery and of 20, 50, and 100 (200) μg into the left coronary artery over 20 s with at least a 3-min interval between each injection. We administered an intracoronary injection of ACh (50/80 μg into the right coronary artery and 100/200 μg into the left coronary artery) just after the ER tests, if a provoked spasm did not occur under the standard single test in 282 cases. When we performed an ACh testing, we inserted a temporary pace maker into the right ventricle of each patient through a femoral or antecubital vein and the pacing rate was set at 45 beats/min. We have no experiences of intravenous injection of ER. We experienced 14 serious major complications (0.84%) with ACh tests including four ventricular fibrillations, one sustained ventricular tachycardia, six cardiogenic shocks, two severe hypotensions and one cardiac tamponade, and four serious major complications (0.34%) with ER tests including two ventricular fibrillations and two cardiac arrests. Serious major complications during selective pharmacological spasm provocation tests in our experiences were 0.57% (16/2828). However, we experienced no cardiac death, acute myocardial infarction, or coronary aorta bypass graft surgery during the spasm provocation testing over 24 years.

In this review, we defined the serious major complications as ventricular fibrillation, ventricular tachycardia, bradycardia, cardiogenic shock, cardiac tamponade, acute myocardial infarction, coronary aorta bypass graft surgery, and death.

Complications of intravenous ER test

Maximal intravenous injection of ER was 0.4 mg in the majority of the past studies [8,19–28]. As shown in Table 1, serious major complication rate with intravenous ER test was 0.31% (26/8419). Buxton et al. reported five serious major complications including three deaths and one coronary aorta bypass graft surgery [8]. However, other reports had no deaths or coronary aorta bypass graft surgery. Ventricular tachycardia and ventricular fibrillation was observed in 15 patients (0.18%), while bradycardia was recognized in 4 patients (0.05%), and cardiogenic shock was found in 10 patients (0.12%). Harding et al. also reported four patients suffering from acute myocardial infarction after intravenous ER tests [28]. Complications of acute myocardial infarction, coronary aorta bypass graft surgery, and death were observed in eight patients (0.1%). Cardioversion was necessary to recover sinus rhythm in four patients (0.05%).

Complications of intracoronary ER test

Total intracoronary injection of ER was approximately 50 μg in each coronary artery in past studies [29–32]. Serious major complications were recognized in 0.51% (11/2173) of patients with intracoronary injection of ER, as shown in Table 1. Neither death nor coronary aorta bypass graft surgery was reported. Moreover, no acute myocardial infarction was recognized. Ventricular tachycardia and ventricular fibrillation were observed in nine patients (0.41%), while bradycardia was found in six patients (0.28%). Electric countershock was necessary to recover sinus rhythm in five patients (0.23%).

Complications of ACh test

Under the temporary pacemaker insertion, ACh was injected in incremental doses of 20, 50, and 80 μg into the right coronary artery and 20, 50, and 100 (200) μg into the left coronary artery over 20 s with at least a 3-min interval between each injection in